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Dynamic Susceptibility Contrast (DSC) Perfusion MR in the Prediction of Long-Term Survival of Glioblastomas (GBM): Correlation with MGMT Promoter Methylation and 1p/19q Deletions

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Original Article

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Purpose: To investigate the surgical, perfusion, and molecular characteristics of glioblastomas which influence long-term survival after treatment, and to explore the association between MR perfusion parameters and the presence of MGMT methylation and 1p/19q deletions.

Materials and Methods: This retrospective study was approved by our institutional review board. A total 43 patients were included, all with pathologic diagnosis of glioblastoma with known MGMT methylation and 1p/19q deletion statuses. We divided these patients into long-term (≥ 60 months, n = 7) and short-term (< 60 months, n = 36) survivors, then compared surgical extent, molecular status, and rCBV parameters between the two groups using Fisher's exact test or Mann-Whitney test. The rCBV parameters were analyzed according to the presence of MGMT methylation and 1p/19q deletions. We investigated the relationship between the mean rCBV and overall survival using linear correlation. Multivariable linear regression was performed in order to find the variables related to overall survival.

Results: Long-term survivors (100% [7 of 7]) demonstrated a greater percentage of gross total or near total resection than short-term survivors (54.5% [18 of 33]). A higher prevalence of 1p/19q deletions was also noted among the long-term survivors (42.9% [3 of 7]) than the short-term survivors (0.0% [0 of 36]). The rCBV parameters did not differ between the long-term and short-term survivors. The rCBV values were marginally lower in patients with MGMT methylation and 1p/19q deletions. Despite no correlation found between overall survival and rCBV in the whole group, the short-term survivor group showed negative correlation (R^2 = 0.181, P = 0.025). Multivariable linear regression revealed that surgical extent and 1p/19q deletions, but not rCBV values, were associated with prolonged overall survival.

Conclusion: While preoperative rCBV and 1p/19q deletion status are related to each other, only surgical extent and the presence of 1p/19q deletion in GBM patients may predict long-term survival.

Keywords: Original research; Glioblastoma; Perfusion imaging; Magnetic resonance image, Dynamic susceptibility contrast perfusion; Radiogenomics

INTRODUCTION

Glioblastoma (GBM) is a rapidly progressing type of primary malignant brain tumor with a mean survival of less than 15 months, with only 3-5% of patients surviving longer than five years after diagnosis (1, 2). Even in the case of surgical resection followed by radiotherapy, most GBM patients die within two years from the date of diagnosis, and little improvement in brain tumor survival had been achieved until the development of chemotherapy with temozolomide (TMZ), a DNA alkylating agent. Combining radiotherapy with TMZ has been shown to improve prognosis and increase overall survival in high grade glioma patients (3-9).

In the past, the classification of gliomas has been solely based on histological phenotypes. However, an increasing body of knowledge on genomics has supported the idea that the subtyping of gliomas based on their genetic parameters demonstrates better correlation with prognosis than did conventional histological subtyping (10). Accordingly, recently revised WHO classification of gliomas suggested glioma classification based upon not only the well-established histologic criteria but also upon the genetic characteristics (11, 12). Of the various genetic markers related to gliomas, methylation status of O-6-methylguanine-DNA methyltransferase (MGMT) gene promoter and the status of 1p/19q deletion have been suggested to be related to tumor prognosis (13, 14). Methylation of the MGMT promoter results in decreased levels of MGMT protein, a DNA repair enzyme, thereby precipitating tumor cell death. Recent studies have also suggested that the methylation of MGMT promoter enhances sensitivity to chemotherapy, thus improving prognosis with prolonged survival in high-grade glioma patients undergoing chemotherapy with TMZ (15, 16). On the other hand, co-deletion of 1p19q is a required marker for the diagnosis of 'canonical oligodendroglioma' and for the subclassification of GBM. Accordingly, the presence of 1p19q codeletion in glioblastoma is demonstrated in GBMs with oligodendroglioma background, which are known to have better prognoses than classical GBMs (14, 16). Nevertheless, there have been conflicting results as to the relationship or lack thereof between these two genetic/epigenetic alterations and the prognosis of GBM (17, 18).

Despite the huge advantage of genetic profiling of GBM for prognostication, genomic information from the part of GBM is inherently inadequate and does not represent the status of the whole GBM, which necessitates the use of a non-invasive procedure for the prognostic prediction of GBM. Segmentation methods using structural images such as T2-weighted images or contrast-enhanced T1-weighted images have demonstrated clinical utility in the measurement of apparent diffusion coefficient (ADC) values from glioblastomas (19). Additionally, by using perfusion dynamic susceptibility contrast (DSC) MRI, differential diagnosis between glioblastoma and primary central nervous system (CNS) lymphoma can be achieved with a high diagnostic confidence (20). While perfusion DSC-MRI has shown a strong correlation between glioma grade and rCBV values (21), the relationships between DSC perfusion parameters and genetic markers/overall survival are not straightforward (22, 23). Beyond MRI, clinical factors, such as the extent of resection, are regarded as important prognostic factors for GBM (24).

Therefore, we aimed in this study to compare the perfusion characteristics of GBMs between long-term (≥ 60 months) and short-term (< 60 months) survivors using DSC-MR perfusion imaging, and aimed to investigate its association with MGMT promoter methylation and 1p/19q deletion status of GBM, as well as whether preoperative DSC parameters are predictive of survival of GBM.

MATERIALS AND METHODS

Subjects

This retrospective study was approved by our institutional review board, and informed consent was waived as it was a retrospective study. Forty-five patients with pathologic diagnoses of glioblastoma (WHO grade IV) on postoperative specimen from January 2010 to August 2015 were identified. The MGMT promoter methylation and 1p/19q deletion statuses from each patient were recorded based on their final pathology reports. Two patients were excluded because their data on MGMT promoter methylation or 1p/19q deletion profile was missing. As a result, a total of 43 patients (26 male and 17 female; mean age, 56.4; age range, 14-89 years) were included for baseline analysis.

The overall survival (in months) of each patient was calculated from the date of initial brain MRI to either the date of the last clinic visit or the date of death. We divided the patients into two groups: long-term survivors (≥ 60 months) and short-term survivors (< 60 months) (16) (Table 1).

Perfusion MR imaging analyses were performed in 29 of 43 patients, because 14 patients were excluded due to the loss of raw perfusion MR data (Fig. 1). All GBMs were

confirmed at the time of biopsy (n = 1), partial resection (n = 1), subtotal resection (n = 8), near total resection (n = 8), or gross total resection (n = 11). A neuroradiologist (with 12 years of neuroimaging experience) retrospectively assessed the extent of resection, blinded to clinical information. The extent of resection was classified into one of five categories based on postoperative magnetic resonance imaging as follows: 1) gross total resection (GTR), no visible tumor left; 2) near total resection (NTR), removal of more than 90% but less than 100% of tumor; 3) subtotal resection (STR), removal of 50% to 89% of the tumor; 4) partial resection (PR), removal of 10% to 49% of the tumor; or 5) biopsy (Bx), removal of less than 10% of the tumor (25). The standard treatment protocol included radiation therapy plus continuous daily TMZ (75 mg/m^2 per day) followed by six cycles of adjuvant TMZ (150 mg/m^2 for five days, every 29 days) following surgical resection.

MR Examination

The brain MRI protocol included contrast-enhanced 3D T1 gradient echo images and axial T2* dynamic susceptibility weighted-perfusion that was weighted using 3.0T MRI scanners (GE Healthcare HDxT and Siemens Skyra). Axial T2* DSC-perfusion-weighted imaging (PWI) was performed during the administration of gadobutrol (Gadovist; Schering, Berlin, Germany; 0.1 mmol/kg of body weight) with an injection rate of 3 ml/s followed by a saline flush of 20 cc,

Table 1. Demographic Characteristics of the Study Subjects

Characteristics	Baseline analysis (n = 43)	MR perfusion analysis (n = 29)
Sex		
Male	60.5% (26/43)	55.1% (16/29)
Female	39.5% (17/43)	44.8% (13/29)
Age (years)	56.4 (14-89)*	57.0 (14-89)*
Overall survival (months)		
Long-term survivor (≥ 60 months)	16.3% (7/43)	20.7% (6/29)
Short-term survivor (< 60 months)	83.7% (36/43)	79.3% (23/29)
Genetic markers		
MGMT promoter methylation	48.8% (25/43)	55.1% (16/29)
1p / 19q deletions	7.0% (3/43)	6.9% (2/29)
Surgical extent		
GTR + NTR**	62.5% (25/40***)	65.5% (19/29)
STR + PR + Bx**	37.5% (15/40***)	34.5% (10/29)

Data are number of patients, and data in parenthesis are percentages except where indicated.
*The data is the mean value and the data in parenthesis is range of the values.
** Abbreviations area indicated as follows: GTR = gross total resection; NTR = near total resection; STR = subtotal resection; PR = partial resection; Bx = biopsy
*** 40 of 43 patients were evaluated for surgical extent. Three patients who could not undergo immediate postoperative (< 24 hours) MRI were excluded because the surgical extent could not be accurately measured.

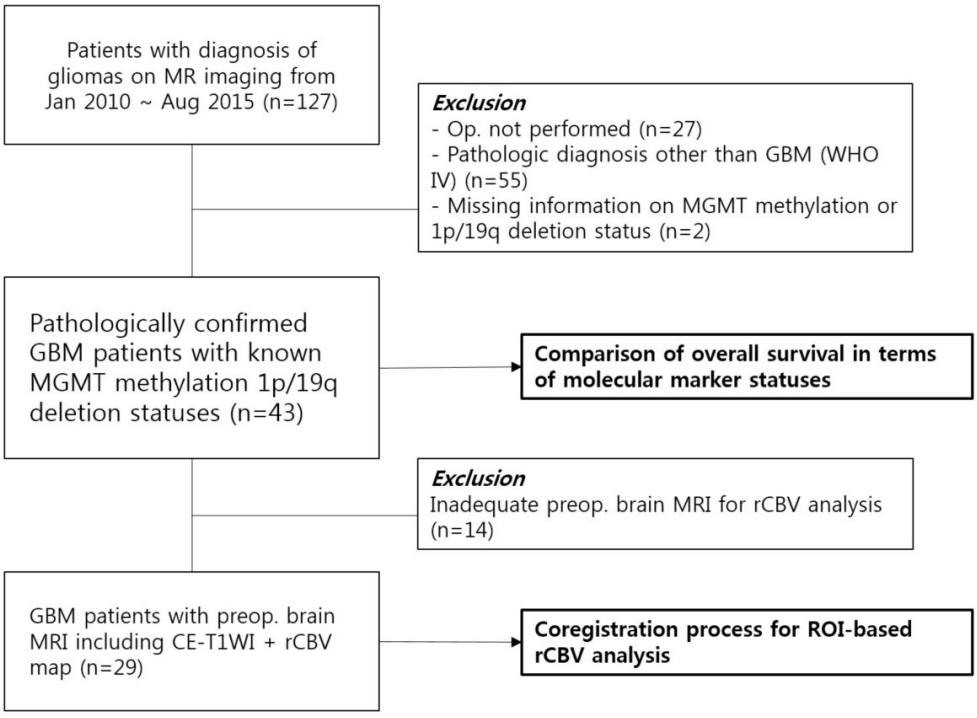

Fig. 1. Study design diagram.

using the single-shot gradient-echo echo-planar imaging sequence (repetition time [TR]/echo time [TE], 1000/18.9 ms; field-of-view [FOV], 240 mm; slice thickness [ST]/interslice gap [IG], 7/0 mm; matrix, 256 × 256; flip-angle [FA], 60°).

Immediately following the acquisition of the DSC-PWI, the post contrast-enhanced 3D fast spoiled gradient-recalled acquisition in the steady state (FSPGR), T1-weighted sequence (TR/TE, 6.2/2.6 ms; FOV, 220 mm; ST/IG, 1/0 mm; matrix, 512 × 512), or 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (TR/TE, 1900/2.46 ms; ST, 0.5 mm; matrix, 256 × 256; FA, 9°) was obtained.

Image Preparation - Coregistration of T1 Contrast-Enhanced MR Images and CBV Map

As the thin-section postcontrast 3D T1 gradient echo images and nCBV map differed in slice thickness, the two images underwent a coregistration process. Following coregistration, the resulting MR images contained both structural and functional information regarding the tumor characteristics. Coregistration was performed using NordicICE (NordicNeuroLab, Norway), a dedicated postprocessing software.

Tumor Delineation and Intratumor Segmentation

After successfully performing the coregistration process, the region-of-interest (ROI) of the enhancing portion of glioblastoma was semi-automatically selected using NordicICE. This ROI selection process was performed by a neuroimaging researcher with three years of neuroimaging experience. Each ROI selection was reviewed by a neuroradiologist (with 20 years of neuroimaging experience) so as to evaluate its adequacy for analysis. After ROI placement was completed in each patient, information pertaining to the brain tumor, such as the volume and surface area of the brain tumor, as well as statistical parameters, such as the mean, median, standard deviation, quartiles, and means of the highest/lowest five percentiles, were calculated using NordicICE.

Statistical Analysis

All statistical analyses were performed using SPSS ver. 20.0. The level of significance was set at $P < 0.05$. All of the continuous variables were tested for normalization.

The difference in frequencies for the extent of surgical resection and for each molecular subtype between long-term/short-term survivors was evaluated with a Fisher's exact test. A Mann Whitney test was performed in order to compare the overall survival (months) according to the status of the extent of surgical resection or genetic alterations, as well as various rCBV parameters, between the long-term and short-term survivors.

Next, in order to explore the relationship between imaging markers (rCBV values) and the two genetic markers, we compared various rCBV parameters (mean, median, 5th percentile, 95th percentile, 1st quartile, 3rd quartile, minimum, and maximum) according to the status of MGMT methylation and 1p/19q deletions.

In order to explore the relationship between overall survival (in months) and mean CBV values, we performed linear regression analysis and a Pearson correlation test.

Finally, we performed multivariable linear regression in order to find variables related to prolonged overall survival. The dependent variable was the overall survival (in months), and the enter method was used in the multivariable regression. The independent variables selected for analysis were the extent of surgical resection, MGMT methylation, 1p/19q deletions, and mean rCBV.

RESULTS

All of the long-term survivors underwent either GTR or NTR (4 GTRs and 2 NTRs), but only 11 of the 23 short-term survivors underwent GTR or NTR. The overall survival was significantly greater in the GTR+NTR group (median, 32 months; interquartile range [IQR], 18-71 months) than in the STR+PR+Bx group (median, 9 months; IQR, 6.5-16 months; $P = 0.00042$).

The long-term survivor group (42.9% [3 of 7]) showed a greater percentage of 1p/19q deletion than did the short-term survivor group (0.0% [0 of 36], $P = 0.037$). As for the percentage of MGMT methylation, no difference was revealed between the long-term (57.1% [4 of 7]) and the short-term survivor groups (58.3% [21 of 36], $P = 1.000$). Between GBM patients with MGMT methylation (median 27.5 months, IQR 15.5-35.5 months) and those without MGMT methylation (median 15 months, IQR 12-40 months), there was no difference found in terms of overall survival ($P = 0.318$). However, 1p/19q deleted GBM patients (median 82 months, IQR 81.5-82.5 months) survived longer than patients without 1p/19q deletion (median 22 months, IQR 11.5-33.5 months, $P < 0.01$) (Figs. 4-6).

Regarding rCBV parameters, there was no significant difference found between the long-term and short-term

survivors (P > 0.05, Table 2). In the context of MGMT methylation, the rCBV values were lower in patients with MGMT methylation. However, this trend was not statistically significant. It should be noted, however, that statistical analysis comparing the rCBV parameters in terms of 1p/19q deletions was inapplicable, due to the small number of 1p/19q deleted patients (n = 2) (Table 3) (Figs. 4-6).

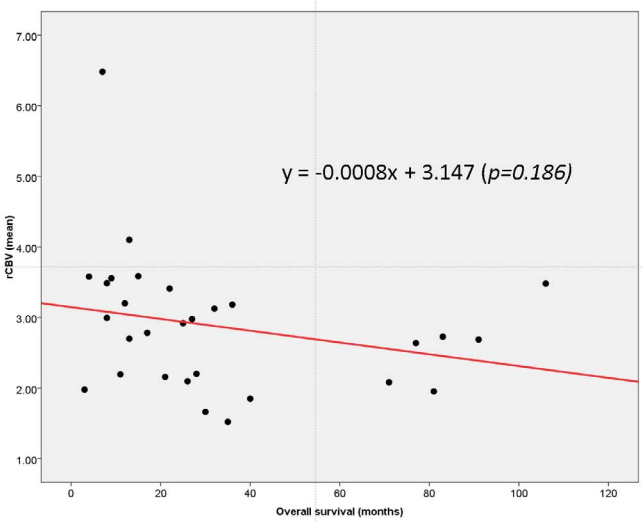

Fig. 2. Scatter plot of mean rCBV versus overall survival (in months) in GBM patients, including both long-term and short-term survivors. Although the scatter plot demonstrates a decreasing trend towards lower mean rCBV values with greater overall survival, the linear regression analysis did not demonstrate a statistically significant linear correlation (P = 0.186, R^2 = 0.029).

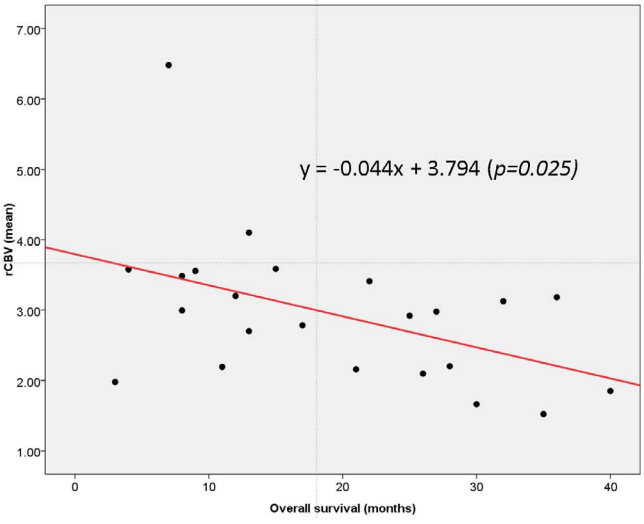

Fig. 3. Scatter plot of mean rCBV versus overall survival (in months) in short-term GBM survivors. Linear regression analysis demonstrated the presence of a statistically significant negative linear correlation between mean rCBV and overall survival (P = 0.025, R^2 = 0.181).

When both the long-term survivor and short-term survivor groups were combined into one large group, there was no significant linear correlation found between the mean rCBV value and overall survival (Fig. 2). However, a significant negative linear correlation was observed between the mean rCBV value and overall survival in the short-term survivor group (adjusted R^2 = 0.181, P = 0.025) (Fig. 3).

Multivariable linear regression analysis demonstrated that our model was able to predict overall survival with statistical significance (P = 0.018, adjusted R^2 = 0.275). Surgical extent and 1p/19q deletion were found to be statistically significant variables contributing to prolonged overall survival (Table 4).

DISCUSSION

We found that the long-term survivor group of GBM was characterized by a higher extent of surgical resection, a higher frequency of 1p/19q deletion and a lower tendency of some rCBV parameters (95th percentile, 3rd quartile, and maximum), but no significant difference was found in terms of median rCBV of the tumor as compared to that of the short-term survivor group.

The findings of our study are in accordance with previous research suggesting that the presence of 1p/19q deletion is a favorable prognostic indicator (26-29). 1p/19q deletion is a hallmark of the presence of an oligodendroglial

Table 2. Comparison of Various rCBV Parameters between the Long-Term and Short-Term Survivors

rCBV parameter	Long-term (n = 6)	Short-term (n = 23)	P-value
Mean	2.66 [1.95-3.48]	2.98 [1.52-6.48]	0.148
Median	2.32 [1.44-3.59]	2.84 [1.58-6.48]	0.430
5th percentile	2.32 [1.44-3.59]	2.84 [1.48-6.48]	0.964
95th percentile	5.71 [3.60-8.09]	7.78 [2.29-12.64]	0.072
1st quartile	1.52 [0.95-2.50]	1.38 [0.00-4.81]	0.693
3rd quartile	3.71 [2.74-5.49]	4.49 [1.87-8.55]	0.072
Minimum	0.03 [0.00-0.18]	0.00 [0.00-1.00]	0.953
Maximum	5.71 [3.60-8.09]	7.79 [2.29-12.64]	0.072

Majority of the rCBV values were lower in the long-term survivor group. However, Mann-Whitney test failed to reveal any statistically significant difference.

Table 3. Comparison of Various rCBV Parameters in Terms of MGMT Methylation and 1p/19q Deletions

rCBV parameter	Group	Group	P-value
MGMT methylation	With MGMT methylation (n = 16)	Without MGMT methylation (n = 13)	
Mean	2.71 [1.52-3.58]	2.99 [1.85-6.48]	0.148
Median	2.63 [1.58-3.68]	2.59 [1.44-6.48]	0.430
5th percentile	0.36 [0.00-1.69]	0.44 [0.00-2.88]	0.964
95th percentile	5.45 [2.29-12.64]	8.09 [3.73-12.52]	0.072
1st quartile	1.37 [0.00-2.95]	1.68 [0.00-4.81]	0.693
3rd quartile	3.74 [1.87-7.07]	5.00 [2.55-8.55]	0.072
Minimum	0.00 [0.00-1.12]	0.00 [0.00-1.07]	0.953
Maximum	5.45 [2.29-12.64]	8.09 [3.73-12.51]	0.072
1p/19q deletion status	With 1p/19q deletions (n = 2)	Without 1p/19q deletion (n = 27)	
Mean	2.34 [1.95-2.73]	2.92 [1.52-6.48]	
Median	1.71 [1.43-2.00]	2.68 [1.44-6.48]	
5th percentile	0.51 [0.50-0.53]	0.43 [0.00-2.88]	
95th percentile	5.84 [3.60-8.09]	6.60 [2.29-12.64]	
1st quartile	1.16 [0.95-1.37]	1.51 [0.00-4.81]	N/A**
3rd quartile	4.11 [2.73-5.48]	4.23 [1.87-8.55]	
Minimum	0.08 [0.00-0.15]	0.00 [0.00-1.12]	
Maximum	5.84 [3.60-8.09]	6.60 [2.29-12.64]	

** Mann-Whitney test was inapplicable in terms of 1p/19q deletions due to limited sample size.

component, and oligodendroglial background in GBM has long been regarded as a predictor for prolonged survival (27). The alteration of 1p/19q has reportedly been linked with greater sensitivity to chemotherapy with alkylating agents (26, 28, 29). However, some reports have not found any improved survival in GBM patients with 1p/19q deletion (30). These conflicting results on the survival of GBM with 1p/19q deletions may be attributable to tumor heterogeneity and the near impossibility of whole tumor analysis of GBM (31).

Unlike 1p/19q deletion, MGMT methylation did not show a statistically significant difference between the long-term and short-term survivor groups in our study. Hegi et al. (13) discussed that MGMT methylation status serves as an independent prognostic factor in GBM patients

Table 4. Multivariate Analysis of Predicting Overall Survival in Terms of Surgical Extent, 1p/19q Deletion, MGMT Methylation, and Mean rCBV

Variables	Adjusted R^2	P-value, univariate	P-value, multivariate
Surgical extent	0.163	0.017	0.042
1p/19q deletions	0.188	0.011	0.039
MGMT methylation	-0.035	0.826	0.490
Mean rCBV	0.029	0.186	0.273

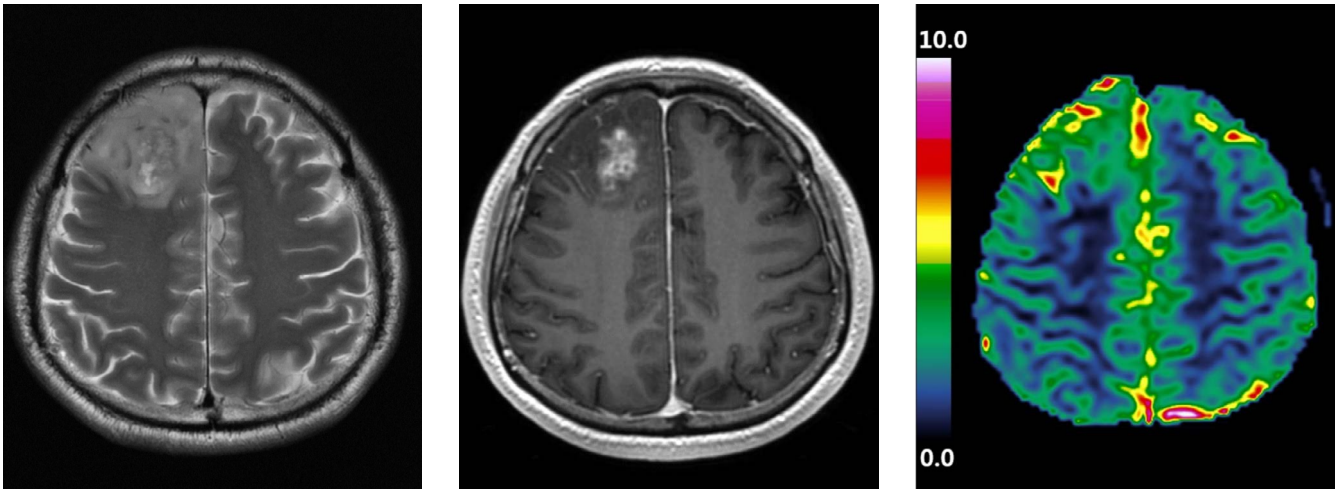

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Fig. 4. A 47-year-old male with glioblastoma in the right frontal lobe. (a) T2-weighted image, (b) T1-weighted contrast-enhanced image, and (c) rCBV map are shown. The mean rCBV value measured from the enhanced part of the tumor was 1.95. Molecular analysis revealed both MGMT promoter methylation and 1p19q codeletion. The overall survival was 81 months.

who undergo chemotherapy with alkylating agent, which contradicts the findings of our study. However, according to a meta-analysis conducted by Meng et al. (32), the prognostic significance of MGMT promoter methylation in terms of overall survival was not as remarkable in the Asian population as it was in the European or American populations. Our study results comparing the proportion of MGMT methylation between the long-term and short-term survivors were in line with Meng's results.

Regarding PWI, the long-term survivor group tended to show lower mean rCBV values (95th percentile, 3rd quartile, and maximum values) than did the short-term survivor group, but this trend was not statistically significant. In a recent study, rCBV was shown to be a significant predictor of progression-free survival both prior to and after anti-angiogenic therapy (33). However, findings on the relationship between rCBV and overall survival, have not been straightforward (34, 35). The tendency of lower

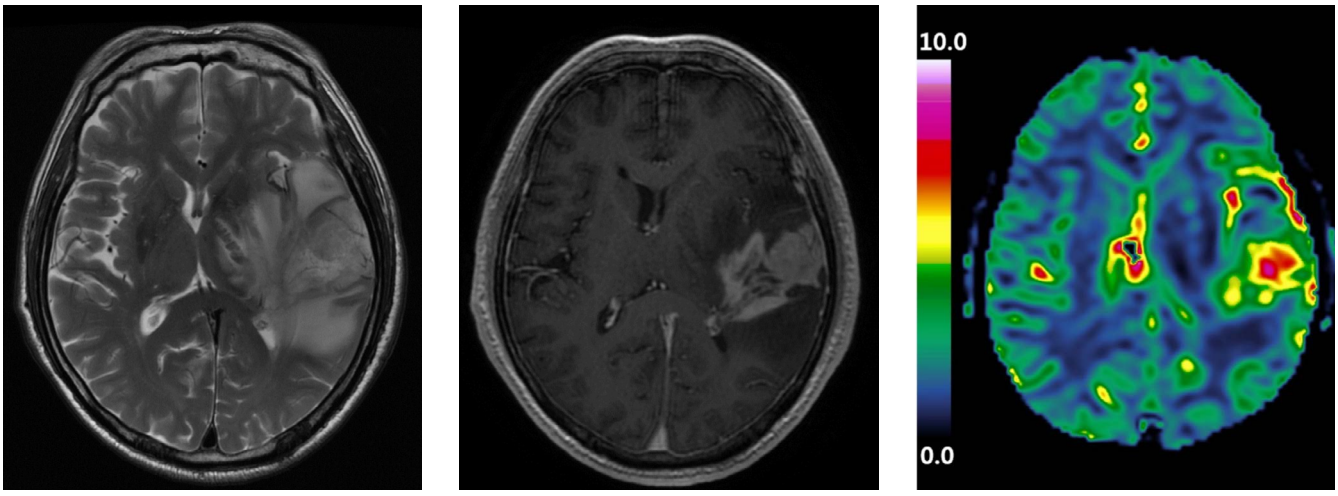

Fig. 5. A 73-year-old male with glioblastoma in the left temporal lobe. (a) T2-weighted image, (b) T1-weighted contrast-enhanced image, and (c) rCBV map are shown. The mean rCBV value measured from the enhanced part of the tumor was 2.70. Molecular analysis revealed that both MGMT promoter and 1p19q were intact. The overall survival was 13 months.

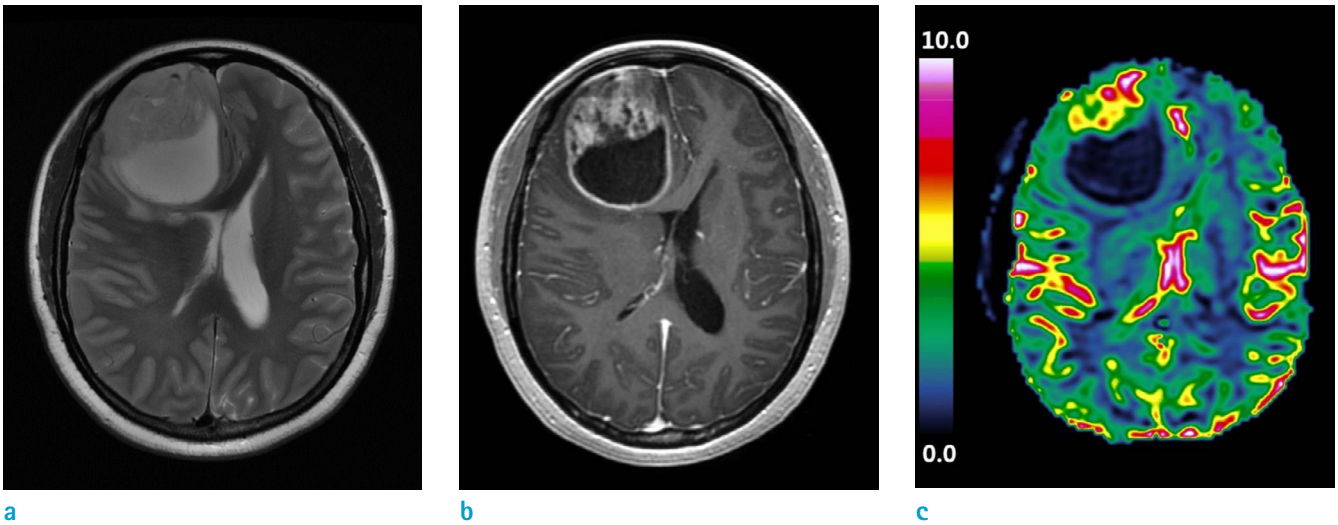

Fig. 6. A 43-year-old female with glioblastoma in the right frontal lobe. (a) T2-weighted image, (b) T1-weighted contrast-enhanced image, and (c) rCBV map are shown. The mean rCBV value measured from the enhanced part of the tumor was 3.48. The molecular analysis revealed that both MGMT promoter and 1p19q were intact. The overall survival was 106 months.

mean rCBV values found in our long-term survivor group may suggest a complex role of rCBV and vascularity in the overall survival of GBM.

In terms of the relationship between genetic markers and imaging markers, we found that GBM patients with 1p/19q deletion showed longer survival than those without 1p/19q deletion. Moreover, despite a limited sample size, 1p/19q deleted patients seemed to demonstrate lower CBV values overall. This result appears to be somewhat counterintuitive, given that the presence of 1p/19q deletion, a molecular marker for oligodendroglial background, is related to higher rCBV values (36, 37). In a study comparing rCBV values between WHO grade II astrocytoma and WHO grade II oligodendroglioma (36), a higher average rCBV value was noted in the oligodendrogliomas. In another study comparing rCBV between oligodendroglial tumors with 1p/19q deletion and those with intact 1p/19q, the presence of 1p/19q deletion was related to higher rCBV (37). Unlike previous studies, our study only included the GBM patients in which 1p/19q deletion could not be determined with the same accuracy as the low-grade oligodendrogliomas, due to tumor heterogeneity of GBM (17). A further study with a larger case series is warranted in the near future.

GBM patients with MGMT methylation demonstrated lower rCBV values than nonmethylated patients, although this trend was not statistically significant. These findings were consistent with those of a previous study showing that the MGMT status of GBM was not related to the rCBV (15).

In our study, the relationship between the overall survival and the mean CBV did not represent a completely linear function. When short-term survivors are considered separately, however, the lower values of rCBV tended to correlate with prolonged survival. According to Bonekamp et al. (38), preoperative perfusion MRI showed that an elevated CBV value was associated with worse overall survival. Interestingly, Bag et al. (22) demonstrated that there was a statistically significant association between posttreatment perfusion parameters and overall survival (OS), but that there was no such association between pre-treatment perfusion parameters and OS. In our study, multivariable linear regression even confirmed that surgical extent and 1p/19q deletion are the only meaningful prognostic factors for glioblastoma overall survival. Thus, our results contradict those of the recent systemic review claiming that rCBV is a good predictive/prognostic marker (pooled hazard ratio of 0.47 for overall survival) (23). A further study with a larger sample size for the long-term survivor group is needed in the future in order to address these conflicting results.

This study has several limitations: The first limitation is the retrospective nature and small sample size of the study. The second limitation is that this study focused mainly on the association between rCBV parameters measured on tumor ROIs and their molecular subtypes. Other factors that might have influenced patient survival, such as the socioeconomic status and general condition of each patient, were not extensively taken into account. Statistical analysis in terms of 1p/19q deletion was inapplicable due to a small sample size (n = 2). However, our 1p/19q-deleted patients demonstrated prolonged overall survival and lower rCBV values than did 1p/19q nondeleted patients.

We believe our findings demonstrate the significance of perfusion parameters of GBMs and its relationship to genetic parameters such as MGMT methylation and 1p/19q deletion status in terms of the overall survival of GBM patients.

In conclusion, our study showed that being a long-term survivor (≥ 60 months) of GBM is significantly associated with surgical resection and 1p/19q deletion status of the tumor, as well as a tendency of lower rCBV (95th percentile, 3rd quartile, and maximum) values of preoperative PWI, but this trend is not statistically significant. Surgical extent and the presence of 1p/19q deletion in GBM patients may predict long-term survival.

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